EVALUATION OF SYNTHETIC CHROMONE, COUMARIN DERIVATIVES AND THEIR POLYMERIC COMPOSITES FOR BIOLOGICAL AND OPTOELECTRONIC APPLICATIONS

SYNOPSIS

OF THE Ph.D. THESIS TO BE SUBMITTED

TO

MANGALORE UNIVERSITY

FOR THE AWARD OF DEGREE OF

DOCTOR OF PHILOSOPHY

IN

INDUSTRIAL CHEMISTRY

BY

B S DAYANANDA

DEPARTMENT OF INDUSTRIAL CHEMISTRY

MANGALORE UNIVERSITY

MANGALAGANGOTHRI-574199

SEPTEMBER 2024

Name of candidate:	**Mr. B. S. DAYANANDA**
Title of the thesis:	**Evaluation of synthetic chromone, coumarin derivatives and their polymeric composites for biological and optoelectronic applications**
Name of the guide:	**Prof. B. K. Sarojini**
Name of the institution:	**Department of Industrial Chemistry** **Mangalore University, Mangalagangothri**
Registration No:	**MU/EXB/Ph.D./CR.31/Ind.Chem./2021-22/E.25**
Registration date:	**11/09/2019**
Pre-colloquium Date:	**29/06/2024**

The thesis entitled "Evaluation of synthetic chromone, coumarin derivatives and their polymeric composites for biological and optoelectronic applications" has been divided into six chapters

Chapter 1: An overview on the applications of synthetic chromone, coumarin derivatives, and their polymeric composites

Chapter 2: Synthesis and characterization of chromone and coumarin derivatives

Chapter 3: Biological activities of chromones with transdermal drug delivery through electrospun cellulose acetate nanofibers

Chapter 4: Coumarin-cellulose acetate composites as electrospun nanofiber mats for transdermal delivery patches

Chapter 5: Aggregation-induced emission in pullulan-chromone derivative electrospun nanofiber composites

Chapter 6: Fluorescent activities of chitosan-coumarin derivative composite films

Chapter 1

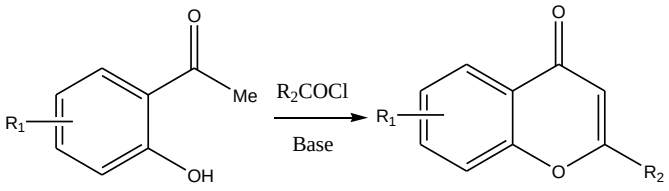
An overview on the applications of synthetic chromone, coumarin derivatives, and their polymeric composites

1.1 Introduction

Chromone (benzopyran-4-one) and coumarin (benzopyran-2-one) are the two main heterocyclic compounds that have grabbed attention due to their extraordinary biological and fluorescent applications. Their occurrence in nature as plant products and their biocompatible, non-toxic nature have made researchers to synthesize them in the laboratory by adopting various synthetic routes. They have several attractive features such as low molecular weight, simple structure, high bioavailability, and high solubility in most organic solvents, together with multifaceted biological activities, ensuring a prominent role as lead compounds in drug research and development. Fluorescent coumarin and chromone colorants show promising photophysical and photochemical properties, reasonable stability, good solubility, and relative ease of synthesis. The fluorescent activities of the chromone and coumarin derivatives have been greatly influenced by the nature of the substituents present in the molecule. It is always encouraged to modify the structure of the fluorescent molecules to achieve the desired fluorescent properties.

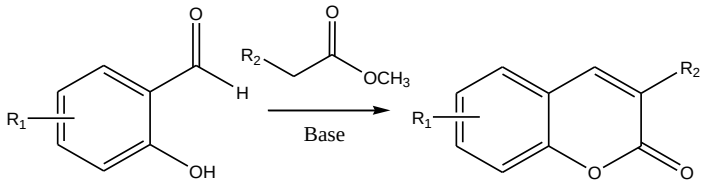
1.2 Synthesis of chromone and coumarin derivatives

Traditionally, chromones were prepared from corresponding *o*-hydroxy benzophenone derivatives with acyl chloride via condensation reactions. The reaction proceeds via esterification and Baker-Venkataraman rearrangement, promoted by potassium t-butoxide. The intermediate esters were treated with a base for acyl transfer reaction, and subsequent dehydration afforded chromones with moderate yields (Scheme 1.0). It is also prepared by starting from *o*-hydroxy acetophenone via the Algar-Flynn-Oyamada (AFO) reaction. [1]



Scheme 1.0 Synthetic route of chromones

Coumarins could be synthesized with many different methods namely the Perkin reaction, Knoevenagel condensation, Pechmann condensation, Wittig reaction, Baylis-Hillman reaction, Claisen rearrangement, Vilsmeier-Haack and Suzuki cross-coupling reactions. The synthetic methods have been modified according to the sensitivity of the substrate to make the synthetic route more efficient.



Scheme 1.1 Synthetic route of coumarins (Knoevenagel condensation)

The ability of chromone and coumarin derivatives to interact with the biological system and their therapeutic effects during various pathological conditions of the body evidences its importance in the field of biomedicine. The peculiar innate structural, chemical, and physical properties of the aforementioned derivatives contributed to various biological activities that have enabled them to be used as antiviral, antioxidant, anti-inflammatory, and anti-cancer agents.

1.3 Biological importance of chromone derivatives

The 3-hydroxy flavone is a derivative of chromone possessing the hydroxyl group at the 3rd position. Its structural feature has the flexibility to be used in both biological and fluorescent applications. Several flavonols have been reported to have anti-inflammatory activity with minimal side effects. Luteolin and apigenin are known anti-inflammatory agents in treating inflammatory diseases through various mechanisms.[2] Luteolin displayed anti-inflammatory activity by inducing more HO-1 gene expression through Nrf2 signaling to protect cells from numerous inflammation-related pathological conditions whereas apigenin showed pharmacological effect by suppressing nitric oxide production. The position and number of hydroxyl groups on the flavone ring system can alter the degree of anti-inflammatory activity.[3] It is proven that chrysin (5,7-hydroxy flavone) inhibits nitric oxide (NO) production at a lower IC_{50} value than 7-hydroxy flavones, revealing that flavone containing hydroxyl group at the 5^{th} position tends to contribute towards anti-inflammatory activity. Luteolin and Nepetin possess hydroxyl groups in the 6^{th} and 7^{th} positions of ring A respectively, but they display anti-inflammatory activity through different mechanisms at different IC_{50} values.[4]

Nepetin alleviates inflammatory responses of human retinal pigment epithelial (ARPE-19) cells persuaded by interleukin (IL)-1β.

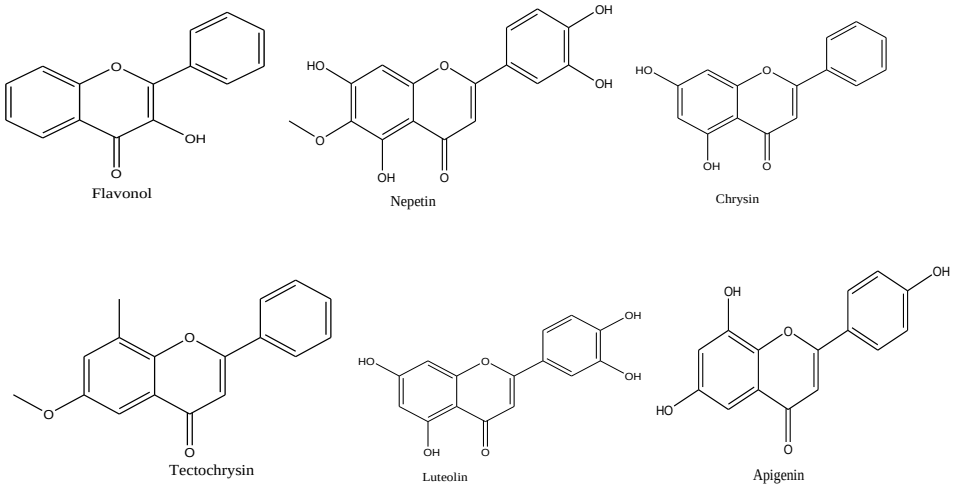


Figure 1.0 Structure of biologically important chromone derivatives

1.4 Biological activities of coumarin derivatives

Similarly, the coumarin derivatives have known for their potential therapeutic values and the many derivatives have been established their commercial values in the market [5]. Novobiocin and fraxetin are antibiotics derived from coumarin and found to be effective against gram positive bacteria.[6][7] Umbelliferon is known for its antibiotic, antifungal, antibacterial and anticancer activities.[8] Coumarin derivative warfarin is a widely acceptable oral anticoagulant to prevent blood clot formation.[9] They work by inhibiting the synthesis of vitamin K-dependent clotting factors in the liver. Esculetin displayed anti-inflammatory activity by inhibiting the activity of prostaglandin and leukotriene [10].

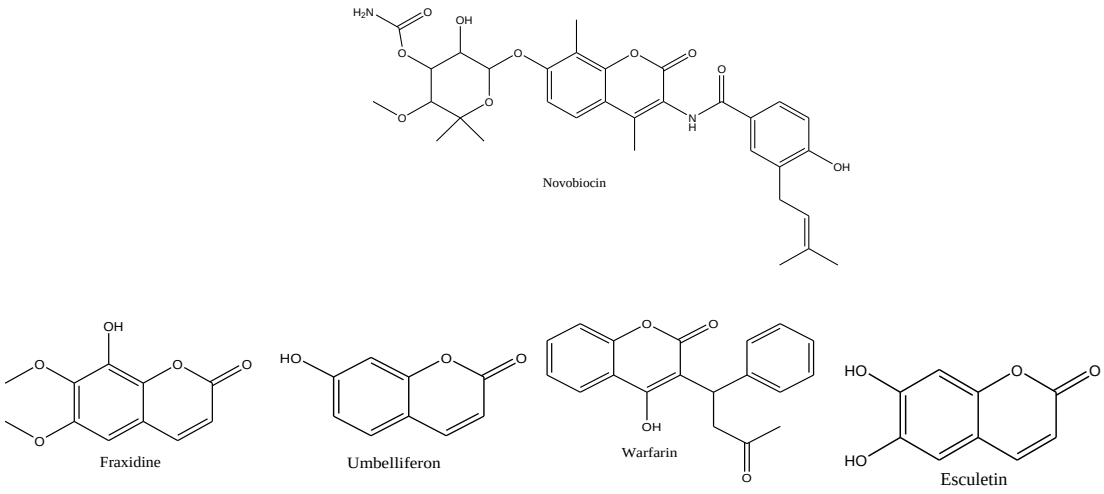


Figure 2.0 Structure of biologically important chromone derivatives

1.5 Transdermal drug delivery applications by electrospun nanofibers

The mode of delivery of all aforementioned drugs plays a vital role in the effective delivery of the drug to the targeted site. Different formulation methods have been adopted by various researchers for the successful delivery therapeutic agents [11][12][13]. To make the delivery of these drugs to the targeted site, the drug should be delivered in the composite form to enhance the treatability of any pathological condition. The transdermal drug delivery system is most commonly used to deliver the drug candidate for wound healing applications [14][15]. The fibrous electrospun polymer matrices gained remarkable attention due to the easy fabrication process, high surface-to-volume ratio, oxygen permeability, exchange of exudates without accumulation, and smooth and uniform adherence *in situ.* This electrospun nanofibrous mat could accelerate the wound-healing process by reducing necrosis and enhancing vascularization. Cellulose acetate is a well-known polymer and has been utilized by various researchers for wound-healing applications.[16][17][15] Several types of wound dressings have been produced using cellulose-based biomaterials, and the results have been encouraging. Biocompatibility and *in vivo* physicochemical qualities are critical for an optimal wound dressing[18].

1.6 Fluorescent applications of polymer/organic dopant matrix

The chromone and coumarin derivatives are well received for their florescent activities. Many scintillating materials have been designed by combining fluorescent material (3HF) with a polymer matrix [19] [20] [21]. The polymer matrix could mechanically support the organic fluorophore along with the synergetic enrichment of the photophysical properties of the developed material. The choice of the right and apt polymer plays a crucial role to design the practically valuable optical material.

1.7 Pullulan as polymer matrix for composites

Pullulan nanofiber has been well-documented for its usage in drug delivery systems and food packaging applications [12]. This structural aspect imparts unique physical properties to form strong, transparent, and water-soluble films [22]. More often, pullulan is blended or doped with other polymers or materials to modify its property [23]. The polymer is soluble in an aqueous medium even at quite high concentrations without showing any gelation. The successful removal of water from the pullulan provides transparency to it. Being transparent in nature, the pullulan nanofiber is of great interest in optical materials. Unlike other polymers used for optical materials, pullulan is biodegradable and biocompatible which makes it even more

suitable for the optical application. The optical property of the pullulan nanofiber could be modified by the same technique by incorporating a fascinating organic fluorophore. The optical applications of pullulan are hardly examined and the report on the optical application of pullulan nanofiber is not yet explored.

1.8 Chitosan as polymer matrix for composites

The chitosan being nonfluorescent in nature, the optical applications have been limited to some extent. However, the modification or functionalization of chitosan has paved the way for engineering optically exciting materials. The photosensitive chitosan-anthracene carboxaldehyde had been reported as an energy transfer material [24]. The chitosan crosslinked thiophene carboxaldehyde film had proven to be potential nonlinear optical material. The hybrid chitosan/1,3,4-oxadiazole derivative thin film was reported to possess fluorescent properties [25]. The gamma irradiation technique also had been explored to cross-link the carbazole and oxadiazole derivatives with chitosan to develop as emissive materials [26]. The chitosan either can be doped with optically attractive organic small molecules or could be chemically modified due to the presence of an easily accessible and highly reactive amine group.

The emission behaviour of dopant in the polymer matrix could be controlled by the orientation of the dopants and the microenvironment present in matrix. The arrangement of dopant molecules in the polymer matrix decides the type of emission to be taken place from the composite system. The molecules could take up different aggregation patterns namely H-aggregation, X-aggregation, or J-aggregation owing to their crystal packing in the lattice.[27],[28] The crystal packing may get disturbed due to the microenvironment present in the polymer matrix causing substantial changes in the absorption or emission behavior or may remain intact upon incorporation into the matrix. The limited literatures could be seen on aforementioned topic and possess great scope to investigate the behaviour of fluorescent dopants in polymer matrix.

Research Gap

Even though the chemistry of chromone and coumarin derivatives is well established, their uses could be further investigated in composite forms. So, investigating chromone and coumarin derivatives in polymer matrix for biological and optical properties could open up new insights into their property which would lead to newer applications. The therapeutic use of the biologically active molecule is enhanced when it is delivered to the targeted site. The polymers offer themselves as promising matrices for the controlled delivery of drugs into targeted sites. Meanwhile, the fluorescence properties of the molecules could also vary in their composite forms. However, the interaction of fluorophores with polymer matrix has not yet been explored completely. In addition, the processability for application of a compound would be easier in composite forms. So, investigating the chromones and coumarins for their biological activity through targeted drug delivery electrospun composite mat possess has a wide scope. The study on the matrix dopant interaction to tailor emission properties of composites also has a great advantage to cater the need in optoelectronic and photonic fields. Based on this, the following objectives have been formed to undertake study for the thesis.

Objectives

- To synthesize potent chromone and coumarin derivatives
- To evaluate the biological activities with transdermal drug delivery applications of electrospun cellulose acetate nanofibers
- To fabricate pullulan matrix with chromone derivatives and study their photophysical properties
- To investigate the photoluminescent activities of chitosan-coumarin derivative composite films

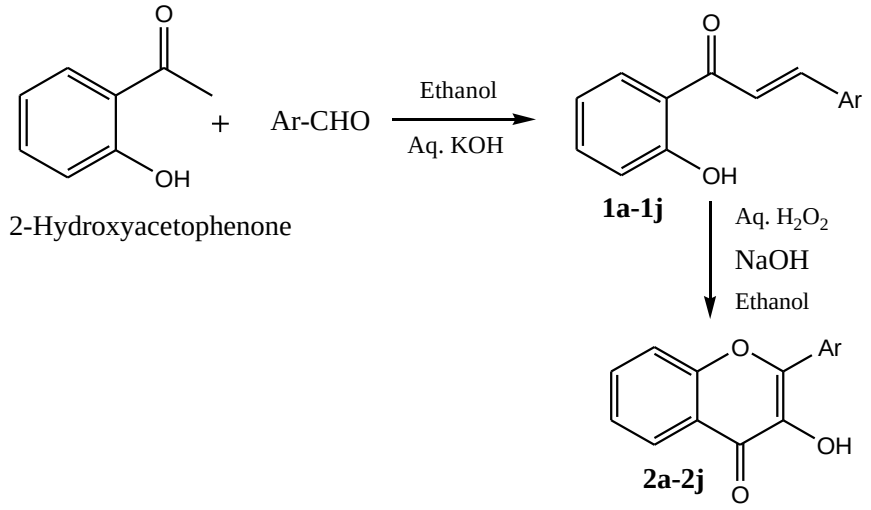
Chapter 2

Synthesis and characterization of chromone and coumarin derivatives

Part A

2.1 Synthesis and characterization of chromone derivatives

3-Hydroxy chromone derivatives were synthesized via Algar-Flynn-Oyamada (AFO) reaction by oxidizing the 2-hydroxy chalcone derivative with hydrogen peroxide in an alkaline medium.

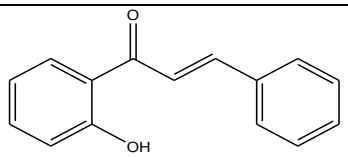
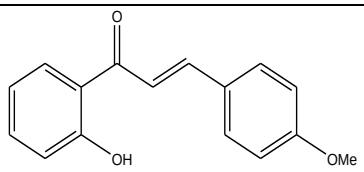
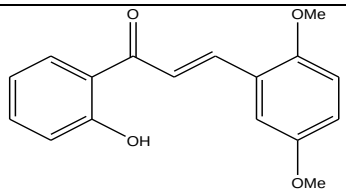
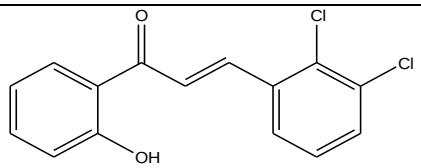
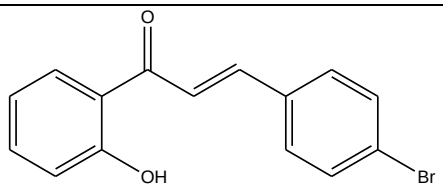
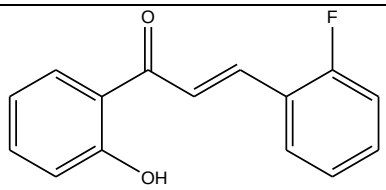
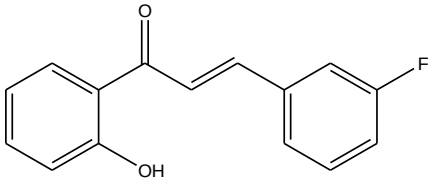


2-Hydroxyacetophenone

Ar = Phenyl, 4-Methoxyphenyl , 2,5-Dimethoxyphenyl, 2-Fluorophenyl, 3-Fluorophenyl, 4-Chlorophenyl, 4-Bromophenyl, 2,3-Dichlorophenyl 2-Thiophene, 5-Bromo-2-thiophene

Scheme 2.1 Synthetic route for the preparation of chromone derivatives

Table 1: Characterization data of 2-hydroxy chalcone derivatives

Compound ID	Structure	Melting point (ºC)	Characterizations
1a		78-80	FT-IR, Mass, ^{1}H-NMR
1b		79-81	FT-IR, Mass, ^{1}H-NMR
1c		96-98	FT-IR, Mass, ^{1}H-NMR
1d		165-167	FT-IR, Mass, ^{1}H-NMR
1e		138-140	FT-IR, Mass, ^{1}H-NMR
1f		82-83	FT-IR, Mass, ^{1}H-NMR
1g		107-108	FT-IR, Mass, ^{1}H-NMR

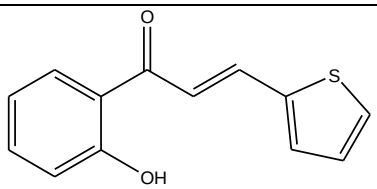
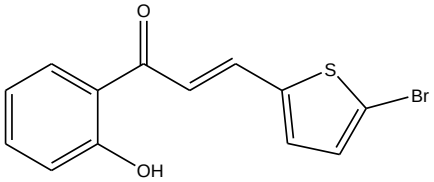
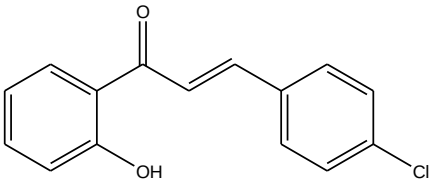
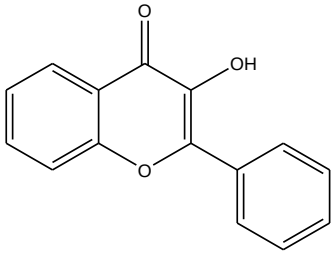
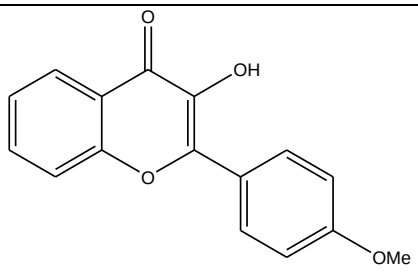
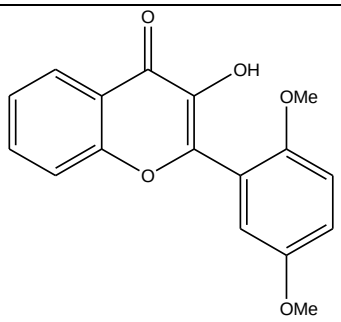
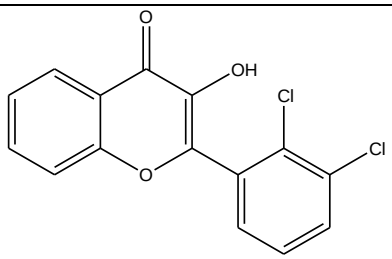
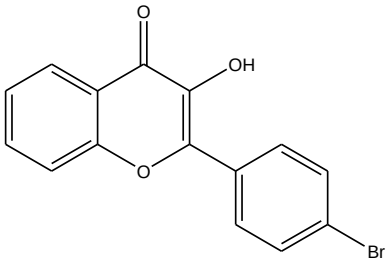
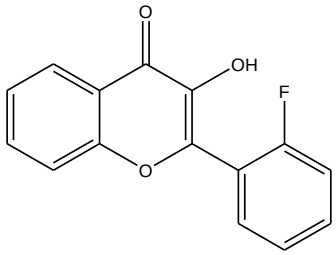
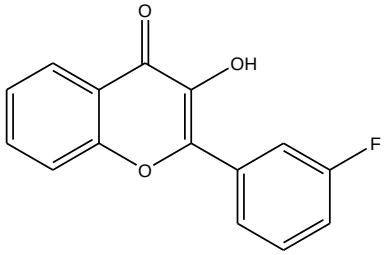
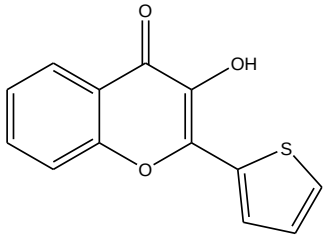
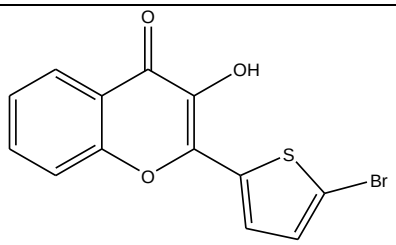
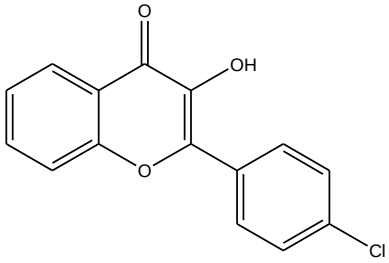
1h		76-78	FT-IR, Mass, ^{1}H-NMR
1i		118-120	FT-IR, Mass, ^{1}H-NMR
1j		145-146	FT-IR, Mass, ^{1}H-NMR,

Table 2: Characterization data of chromone derivatives

Compound ID	Structure	Melting point (ºC)	Characterizations
2a		170-172	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2b		182-184	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR

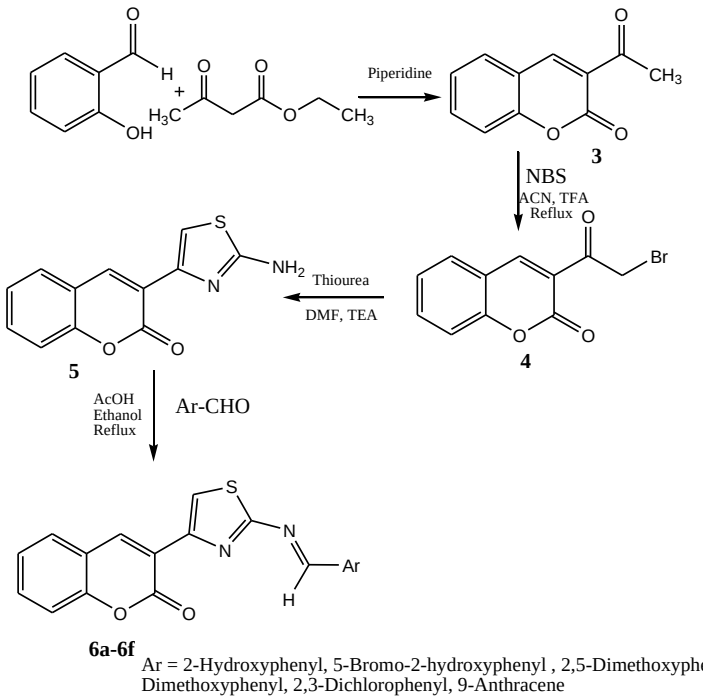
2c		240-242	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2d		162-164	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2e		168-170	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2f		142-144	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2g		150-152	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2h		198-200	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR

2i		242-244	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
2j		154-157	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR

Part B

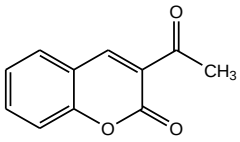
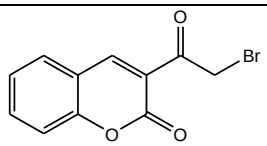
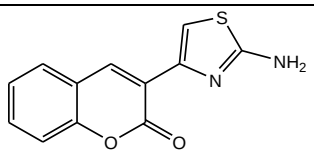
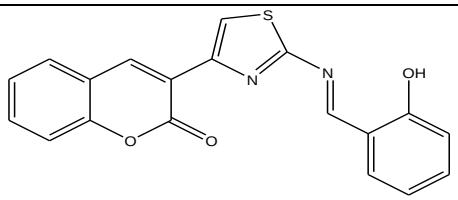
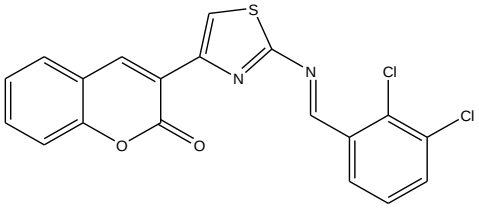
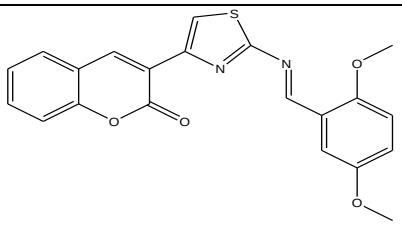
2.2 Synthesis and characterization of coumarin derivatives

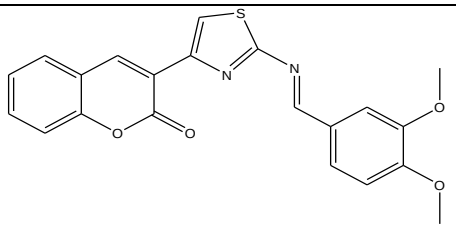
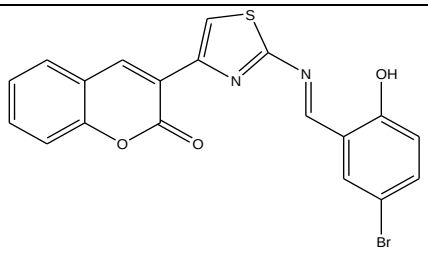
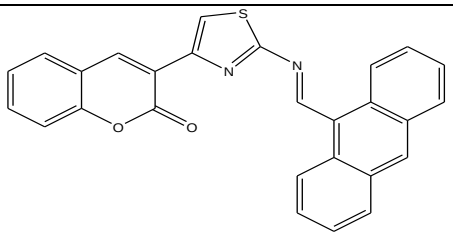
Herein, the coumarin, 3-(2-aminothiazol-4-yl)-2*H*-chromen-2-one, 3-(2-(benzylideneamino)thiazol-4-yl)-2*H*-chromen-2-one derivatives were prepared as depicted in the following scheme



Scheme 2.2 Synthetic route for the preparation of coumarin derivatives

Table 3: Characterization data of coumarin derivatives

Compound ID	Structure	Melting point (ºC)	Characterizations
3		120-122	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
4		165-167	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
5		223-225	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
6a		194-197	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
6b		208-210	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
6c		136-138	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR

6d		178-181	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
6e		258-260	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR
6f		221-223	FT-IR, Mass, ^{1}H-NMR, ^{13}C-NMR

2.3 Conclusion

The chromone derivatives were synthesized through the oxidative cyclization of 2-hydroxy chalcones. The coumarin and coumarin containing thiazole moieties were prepared successfully. Spectral characterizations confirmed the structure of newly synthesized compounds.

Chapter 3

Biological activities of chromones with transdermal drug delivery through electrospun cellulose acetate nanofibers

3.1 Introduction

Modern polymeric drug delivery systems for transdermal therapy are systems which are designed to release drugs to diseased sites of the skin in a consistent and a sustained release manner. The electrospun polymeric nanofibers have considered as drug delivery systems in wound healing, skin burn therapy as topical and transdermal drug delivery systems. The electrospun nanofibers have many advantages such as high surface to volume ratio, porosity and structure that mimics the extracellular matrix. The chromone derivatives are known for their anti-inflammatory activities and display it through various mechanisms. The loading of biologically active candidates into nanofibers have improved their functions.

3.2 Methods

The chromone derivatives **(2a-2j)** were screened for antioxidant activity by DPPH scavenging assay. Th *in-vitro* anti-inflammatory activities were assessed by protein denaturation assy. The derivative with highest activity was evaluated for cytotoxicity and wound scratching assay using NIH3T3 cell line. The same compound was loaded into cellulose acetate nanofiber mat through electrospinning technique. The successful incorporation of the compound in the electrospun mat was confirmed by various analytical and spectral characterisations techniques. The blood compatibility of nanofiber mat and the *in-vitro* delivery of loaded drug was investigated.

3.3 Results

The compound 3-hydroxy-2-(2,5-dimethoxyphenyl)-4*H*-chromen-4-one (**2c)** unveiled good anti-inflammatory (40.11±3.79) and moderate antioxidant activities (30.96±1.34). The wound scratching assay on NIH3T3 cells disclosed the rapid wound healing potential in 18 h. The fabricated cellulose acetate nanofiber's drug encapsulation efficiency was 82.0±1.0% whereas drug release ability was 91.29±0.3% at pH 7.4. The initial rapid release of 37.82±1.3% of the drug was found to be beneficial for quick recovery from the critical phase of symptoms.

3.4 Conclusion

The 3-hydroxy-2-(2,5-dimethoxyphenyl)-4*H*-chromen-4-one [**2c**] was found to be an effective anti-inflammatory agent with moderate antioxidant activity when tested *in vitro*. The good drug encapsulation efficiency and the consequent delivery from the cellulose acetate composite mat was promising. The blood compatibility test indicated the non-toxic nature of the 2c-loaded nanofiber mat and showed the suitability of the nanofiber mat to be employed as an anti-inflammatory wound healing patch in the transdermal drug delivery system.

Chapter 4

Coumarin-cellulose acetate composites as electrospun nanofiber mats for transdermal delivery patches

4.1 Introduction

Coumarin derivatives are of great interest because of their unique structural features and biological activities. Nowadays, many studies are carried out on synthesizing new compounds containing two or more pharmacophore groups to obtain better biological activities. It is also known that hybrids containing two important groups such as coumarin and thiazole have been synthesized and these compounds show wide range of pharmaceutical activities. Apart from their synthesis and biological application, the delivery to the targeted site also crucial to improve their potency and the bioavailability.

4.2 Methods

The coumarin derivatives **(3, 4, 5, 6a-6f)** were evaluated for *in-vitro* antibacterial and anti-inflammatory activities. The derivatives with good antibacterial and anti-inflammatory activities were proceeded further for cytotoxicity studies using NIH3T3 cell line. One derivative was loaded into cellulose acetate nanofiber mat through electrospinning technique. The successful incorporation of the compound in the electrospun mat was confirmed by various analytical and spectral characterisations techniques. The antibacterial activity and blood compatibility of 6e-loaded nanofiber composite mat was studied. Finally, the *in-vitro* drug release from electrospun composite mat was examined to understand the release behaviour of the incorporated drug.

4.3 Results

The coumarin analogues **(3, 4, 5, 6a-6f)** were screened for *in vitro* anti-inflammatory and antibacterial activities. The compounds **6a-6f** displayed good anti-inflammatory activity compared to the control. The evaluation of antibacterial activities revealed that only **5, 6b,** and **6e** could potentially inhibit the bacterial growth. Hence, the compounds that emerged as most active were explored for cytotoxicity studies using the NIH3T3 cell line. To find the application of these derivatives in transdermal drug delivery, the derivative 3-(2-(5-bromo-2-hydroxybenzylideneamino)thiazol-4-yl)-2*H*-chromen-2-one (**6e**) was loaded into cellulose acetate nanofiber using electrospinning technique. The antibacterial activity of the loaded cellulose acetate nanofiber mat was assessed again. It was inferred that 88.29±0.3% of the loaded drug was released throughout 24 h at pH 7.4.

4.4 Conclusion

It was found that the anti-inflammatory activity was improved upon hybridizing the coumarin core with the thiazole moiety. The drug-loaded electrospun composite mat showed promising antibacterial activity with blood compatibility. Hence, the fabricated cellulose acetate nanofiber mat with **6e** would become a potential wound dressing material to due to the anti-inflammatory and antibacterial activities of the loaded compound.

Chapter 5

Aggregation induced emission in pullulan-chromone derivative electrospun nanofiber composites

5.1 Introduction

The chromone derivatives (3-hydroxy flavone) have recently gained enough attention due to distinct dual-emitting behavior. The dual emission property has been under limelight owing to its practical application and could be utilized to design optically important materials. The dual emission is due to the Excited State Intramolecular Proton Transfer (ESIPT) phenomenon instigated by the excited forms of the enol (N*) and keto tautomer (T*). The proton transfer responsible for the ESIPT emission could be partially prevented by a number of parameters, resulting in tunable dual emission behaviour which are extremely reliant on the environment's physical characteristics. The 3-hydroxy flavone derivates could be the better option as a dopant molecule to functionalize the nonfluorescent polymer into an exciting fluorescent material. The

polymer matrix could be doped and hybridized with optically interesting fluorescent molecules via the electrospinning technique or by solvent casting method. The arrangement of dopant molecules in the polymer matrix decides the type of emission to be taken place from the composite system. The molecules could take up different aggregation patterns namely H-aggregation, X-aggregation, or J-aggregation. The crystal packing may get disturbed due to the microenvironment present in the polymer matrix causing substantial changes in the absorption or emission behavior or may remain intact upon incorporation into the matrix.

5.2 Methods

The chromone derivatives 2-(2,5-dimethoxyphenyl)-3-hydroxy-4*H*-chromen-4-one (**2c**) and 2-(2-fluorophenyl)-3-hydroxy-4*H*-chromen-4-one (**2f**) were recrystallized and the single crystals were grown using ethanol as a solvent. The single crystal was characterized to investigate their crystal packing and aggregation pattern. Both the compounds were taken as dopants and doped into a pullulan matrix separately by electrospinning technique. The incorporation of dopants in the pullulan matrix was confirmed by the various analytical techniques such as FT-IR, FESEM, PXRD and TGA. The photophysical property of electrospun pullulan/chromone derivative composite mat was studied using UV spectrophotometer (Shimadzu, Japan) in the 200-400 nm range and Spectro-Fluorophotometer (Shimadzu, Japan). The variation in optical band gap, refractive index, and the quantum yield of the fabricated composite mat was examined.

5.3 Results

The 2-(2,5-dimethoxyphenyl)-3-hydroxy-4*H*-chromen-4-one (**2c**) fabricated electrospun pullulan matrix was investigated to get insights into the aggregation-induced emission of dopant molecule. The composite nanofiber mat was found to possess dopant molecules organized in an X-aggregated fashion accounting for the twisted structure of the dopant molecules. The 2c molecules imparted absorption and emission properties into the fabricated nanofiber mat and turned it to be highly fluorescent triggering yellowish-green emission with a large Stokes shift of 193 nm. On the contrary, the 2-(2-fluorophenyl)-3-hydroxy-4*H*-chromen-4-one (**2f**), owing to the different crystal structure and the interaction, the composite nanofiber mat exhibited a bathochromic shift in absorption profile from 250 nm to 296 nm. The subsequent dual emission at 426 nm (Blue) and 532 nm (Green) was accompanied by the large Stoke's shift value of 90–236 nm. The redshift of the emission profile in the

pullulan/dopant composite mat from 400 nm to 426 nm could be due to the J-aggregation of the dopant molecules in the pullulan matrix. The band gap of the composite nanofiber mat ranged from 2.75 to 3.23. The optimum quantum yield of 32.1–40.3% and enhanced refractive index value suggested the potential application of fabricated pullulan mat as a dual emissive layer in organic light emitting diode (OLED) material which could be an alternative option for multilayer emissive material in OLED device architecture.

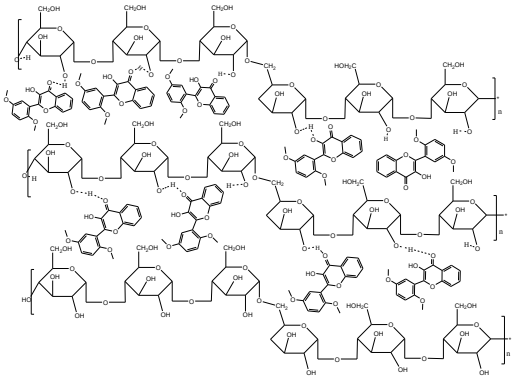


Figure 5.1 Pullulan matrix doped with 2c

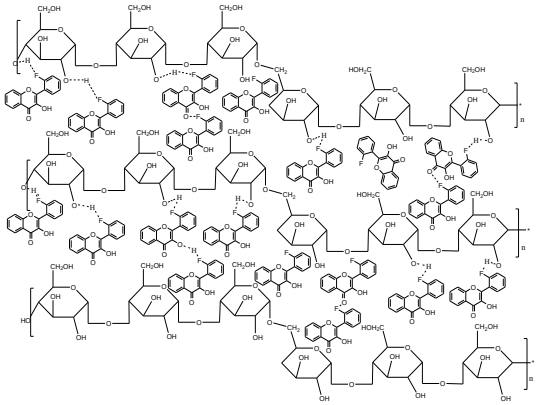


Figure 5.2 Pullulan matrix doped with 2c

5.4 Conclusion:

It was concluded that the dopant structure and the microenvironment nature of the polymeric backbone decides the fate of the photophysical properties of the composite material. The careful selection of dopant and the polymer matrix could be the crucial parameter to modulate the fluorescent properties of the composite mat for desired applications

Chapter 6

Fluorescent activities of chitosan-coumarin derivative composite films

6.1 Introduction

The coumarin moieties are a highly preferable class of heterocyclic compounds to be utilized in the development of fluorescent material. The fluorescent emissions of coumarins have been harvested successfully for various applications. Although many of the coumarin derivatives possess superior fluorescent intensity, the narrow Stoke's shift limits their use as it leads to self-absorption owing to fluorescence quenching. The type and nature of substituents on the coumarin ring control its photophysical properties to a greater extent. It was reported that coumarin could exhibit maximum absorbance and fluorescence emission in a polymeric environment than the solution phase [29]. The fluorescent molecules could be directly doped into the polymer matrix or it could be chemically linked to the polymer backbone to modulate the fluorescent properties. The choice of the right and apt polymer plays a crucial role to design the practically valuable optical material.

6.2 Methods

The photophysical property of chitosan/7-diethylamino-4-methyl coumarin (**F1**) and 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde (**7a**) conjugated chitosan composite film was studied using Ultraviolet-Visible (UV) spectrophotometer (Shimadzu, Japan) and Spectro-Fluorophotometer (Shimadzu, Japan). The variation in optical band gap, refractive index and the quantum yield of the fabricated composite mat was examined. This chapter was divided into two parts. This chapter has been divided into two parts

Part A

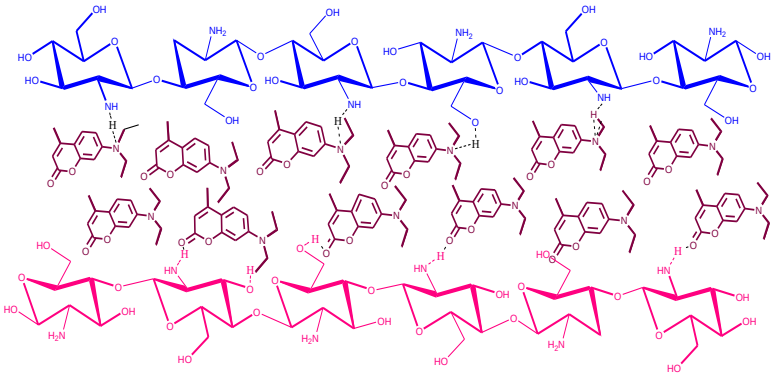


Figure 7.1 Hydrogen bonding interaction between chitosan and DEAMC

6.3 Results

In this part, a blue emissive fluorescent nature of chitosan/7-diethylamino-4-methyl coumarin (F1) composite was studied. The crystal packing of F1 was considered to predict the aggregation of the molecules in the pure and composite systems. In the crystal lattice, the F1molecules aggregated in X-type passion. This interaction between F1 and chitosan matrix could be the reason even for the observed bathochromic shift of the UV absorption band of the F1 molecules from 360 nm to 375nm in the fabricated system. The chitosan/F1 composite film triggered the emission band at 465 nm owing to J-aggregation. The X-aggregation of F1 molecules in its crystal lattice must have switched to J-aggregation due to the polar nature of the chitosan matrix. The calculated direct bandgap was in the range of 2.87-2.93 and the refractive index of 2.11-2.15 inferred that the fabricated composite film was the suitable material to be used as an emissive layer in optical applications.

Part B

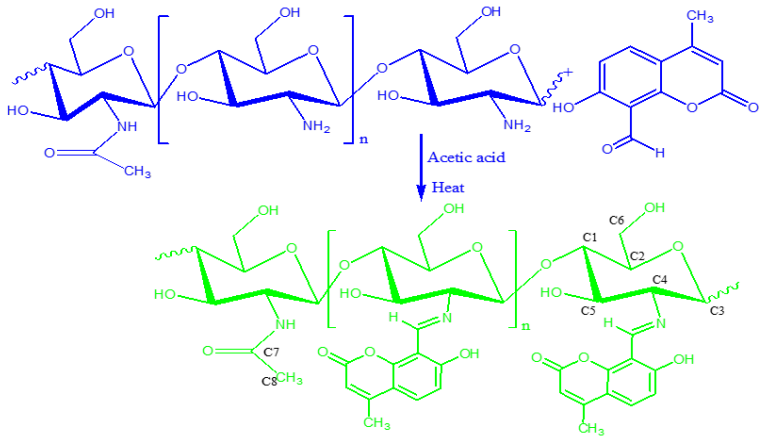


Figure 7.2 Synthetic route for the preparation of 7a-conjugate chitosan

6.4 Results

Here, the greenish-yellow emissive fluorescent coumarin aldehyde conjugated chitosan matrix was prepared by performing a Schiff base reaction between 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde (**7a**) and chitosan. The chemically conjugated chitosan film unveiled a larger Stoke's shift value of 183-224 nm which was just 50–130 nm in pure 7a. The conjugate material could overcome the self-absorption issue associated with the coumarin aldehyde. The 7a exhibited dual emission at 390 nm and 440 nm but it was shifted to 520 nm with single emission upon reaction with chitosan. The observed redshift could be assigned for the formation of static excimer that resulted from the chitosan backbone containing pendant

chromophore (7a) which could interact with another neighbouring chromophoric group of the same chain or different chain creating a ground-state stable dimer. The emission of conjugate material shifted from blue to greenish yellow region with a higher quantum yield of 30.21 % compared to 8.57 % of 7a alone. The calculated direct band gap of 3.20-3.29 and the optimum refractive index suggested the potential optoelectronic applications of 7a-conjugated chitosan as an OLED Material.

6.5 Conclusion

Overall, it was concluded that the crosslinking of fluorescent molecule onto the chitosan backbone impart greater bathochromic shift in the emission spectra of the composite material resulting in the larger Stoke's shift value which could overcome issues associated with self-quenching due to narrow Stoke's shift value.

Outcome

- Total 10 chromone and 10 coumarin derivatives have been synthesized
- In chromone derivatives, the compound **2c** emerged as potent anti-inflammatory wound healing candidate
- The **2c**-loaded cellulose acetate nanofiber mat showed the suitability to be employed as an anti-inflammatory wound healing patch in the transdermal drug delivery system
- In case of coumarin derivatives, the **6e** compound exhibited excellent antibacterial and anti-inflammatory activity and **6e**-loaded electrospun composite mat showed promising antibacterial activity with good level of blood compatibility
- The chromone derivatives **2c** and **2f** doped pullulan nanofiber mat showed dopant structure dependent changes in their optical properties
- The chitosan/7-diethylamino-4-methyl coumarin (**F1**) composite films unveiled the changes in fluorescent property with the blue emission
- The 7a-conjugated chitosan films exhibited the highest Stoke's shift of 183-224 nm with an enhanced quantum yield of 30.21% which was just 8.51% for 7a

References

[1] M. Gharpure, R. Choudhary, V. Ingle, and H. Juneja, "Synthesis of new series of 3-hydroxy/acetoxy-2-phenyl-4H-chromen-4-ones and their biological importance," *Journal of Chemical Sciences*, vol. 125, no. 3, pp. 575–582, 2013, doi: 10.1007/s12039-013-0420-z.

[2] M. Mueller, S. Hobiger, and A. Jungbauer, "Anti-inflammatory activity of extracts from fruits, herbs and spices," *Food Chemistry*, vol. 122, no. 4, pp. 987–996, 2010, doi: 10.1016/j.foodchem.2010.03.041.

[3] S. H. Nile, Y. S. Keum, A. S. Nile, S. S. Jalde, and R. V. Patel, "Antioxidant, anti-inflammatory, and enzyme inhibitory activity of natural plant flavonoids and their synthesized derivatives," *Journal of Biochemical and Molecular Toxicology*, vol. 32, no. 1, 2018, doi: 10.1002/jbt.22002.

[4] H. Matsuda, T. Morikawa, S. Ando, I. Toguchida, and M. Yoshikawa, "Structural requirements of flavonoids for nitric oxide production inhibitory activity and mechanism of action," *Bioorganic and Medicinal Chemistry*, vol. 11, no. 9, pp. 1995–2000, 2003, doi: 10.1016/S0968-0896(03)00067-1.

[5] T. M. Pereira, D. P. Franco, F. Vitorio, and A. E. Kummerle, "Coumarin Compounds in Medicinal Chemistry: Some Important Examples from the Last Years," *Current Topics in Medicinal Chemistry*, vol. 18, no. 2, pp. 124–148, 2018, doi: 10.2174/1568026618666180329115523.

[6] G. M. K. B. Gunaherath, M. T. Marron, E. M. K. Wijeratne, L. Whitesell, and A. A. L. Gunatilaka, "Synthesis and biological evaluation of novobiocin analogues as potential heat shock protein 90 inhibitors," *Bioorganic and Medicinal Chemistry*, vol. 21, no. 17, pp. 5118–5129, 2013, doi: 10.1016/j.bmc.2013.06.042.

[7] S. H. An, G. S. Choi, and J. H. Ahn, "Biosynthesis of fraxetin from three different substrates using engineered Escherichia coli," *Applied Biological Chemistry*, vol. 63, no. 1, 2020, doi: 10.1186/s13765-020-00543-9.

[8] Z. Lin, X. Cheng, and H. Zheng, "Umbelliferon: a review of its pharmacology, toxicity and pharmacokinetics," *Inflammopharmacology*, vol. 31, no. 4, pp. 1731–1750, 2023, doi: 10.1007/s10787-023-01256-3.

[9] A. Popov Aleksandrov *et al.*, "Effects of warfarin on biological processes other than haemostasis: A review," *Food and Chemical Toxicology*, vol. 113, no. August 2017, pp. 19–32, 2018, doi: 10.1016/j.fct.2018.01.019.

[10] Z. Ye *et al.*, "Synthesis and biological evaluation of esculetin derivatives as potential anti-HBV agents," *Medicinal Chemistry Research*, vol. 32, no. 5, pp. 899–909, 2023, doi: 10.1007/s00044-023-03045-7.

[11] M. A. A. S. C. M. J. and; S. J. Sollott, "Drug Delivery Systems and Materials for Wound Healing Applications," *Physiology & behavior*, vol. 176, no. 3, pp. 139–148, 2017, doi: 10.1016/j.addr.2018.04.008.Drug.

[12] A. G. Grigoras, "Drug delivery systems using pullulan, a biocompatible polysaccharide produced by fungal fermentation of starch," *Environmental Chemistry Letters*, vol. 17, no. 3, pp. 1209–1223, 2019, doi: 10.1007/s10311-019-00862-4.

[13] W. T. Arab, A. M. Niyas, K. Seferji, H. H. Susapto, and C. A.E. Hauser, "Evaluation of peptide nanogels for accelerated wound healing in normal micropigs," *Frontiers in Nanoscience and Nanotechnology*, vol. 4, no. 4, pp. 1–9, 2018, doi: 10.15761/fnn.1000173.

[14] Z. Cui *et al.*, "Electrospinning and crosslinking of polyvinyl alcohol/chitosan composite nanofiber for transdermal drug delivery," *Advances in Polymer Technology*, vol. 37, no. 6, pp. 1917–1928, 2018, doi: 10.1002/adv.21850.

[15] A. Gencturk, E. Kahraman, S. Güngör, G. Özhan, Y. Özsoy, and A. S. Sarac, "Polyurethane/hydroxypropyl cellulose electrospun nanofiber mats as potential transdermal drug delivery system: characterization studies and in vitro assays," *Artificial Cells, Nanomedicine and Biotechnology*, vol. 45, no. 3, pp. 655–664, 2017, doi: 10.3109/21691401.2016.1173047.

[16] X. Liu *et al.*, "Antimicrobial electrospun nanofibers of cellulose acetate and polyester urethane composite for wound dressing," *Journal of Biomedical Materials Research - Part B Applied Biomaterials*, vol. 100 B, no. 6, pp. 1556–1565, 2012, doi: 10.1002/jbm.b.32724.

[17] K. Khoshnevisan *et al.*, "Cellulose acetate electrospun nanofibers for drug delivery systems: Applications and recent advances," *Carbohydrate Polymers*, vol. 198, pp. 131–141, 2018, doi: 10.1016/j.carbpol.2018.06.072.

[18] P. Wutticharoenmongkol, P. Hannirojram, and P. Nuthong, "Gallic acid-loaded electrospun cellulose acetate nanofibers as potential wound dressing materials," *Polymers for Advanced Technologies*, vol. 30, no. 4, pp. 1135–1147, 2019, doi: 10.1002/pat.4547.

[19] A. J. Pai, B. K. Sarojini, K. R. Harshitha, and A. Soldera, "Environmentally Benign Blue Emissive Films from Host-Dopant Interaction of PLA–Bischalcone Combination with

High UV Endurance," *Journal of Polymers and the Environment*, vol. 30, no. 1, pp. 373–384, 2022, doi: 10.1007/s10924-021-02196-1.

[20] D. Wahyuningrum, M. Zulqarnaen, and V. Suendo, "The synthesis and characterization of 7-hydroxy-4-methylcoumarin and the investigation of the fluorescence properties of its 7-hydroxy-4-methylcoumarin- chitosan films," *AIP Conference Proceedings*, vol. 1589, no. Icmns 2012, pp. 169–173, 2014, doi: 10.1063/1.4868775.

[21] M. Buffa, S. Carturan, A. Quaranta, G. Maggioni, and G. Della Mea, "Spectral properties of 3-hydroxyflavone embedded in polysiloxane: Effects of the polymerization method," *Optical Materials*, vol. 34, no. 7, pp. 1219–1224, 2012, doi: 10.1016/j.optmat.2012.01.038.

[22] J. ichi Horinaka, Y. Hashimoto, and T. Takigawa, "Optical and mechanical properties of pullulan films studied by uniaxial stretching," *International Journal of Biological Macromolecules*, vol. 118, pp. 584–587, 2018, doi: 10.1016/j.ijbiomac.2018.06.127.

[23] N. N. Bailore, S. K. Balladka, S. J. D. S. Doddapaneni, and M. S. Mudiyaru, "Fabrication of Environmentally Compatible Biopolymer Films of Pullulan/Piscean Collagen/ZnO Nanocomposite and Their Antifungal Activity," *Journal of Polymers and the Environment*, vol. 29, no. 4, pp. 1192–1201, 2021, doi: 10.1007/s10924-020-01953-y.

[24] S. Wu, F. Zeng, H. Zhu, and Z. Tong, "Energy and electron transfers in photosensitive chitosan," *Journal of the American Chemical Society*, vol. 127, no. 7, pp. 2048–2049, 2005, doi: 10.1021/ja045356f.

[25] Pushparekha, B. K. Sarojini, K. Bello, B. S. Holla, and M. M. Subrahmanya, "Design, fabrication and studies on optical properties of new hybrid chitosan films doped with 1, 3, 4-oxadiazole derivatives for down conversion and photoluminescence applications," *Optical Materials*, vol. 89, no. September 2018, pp. 80–91, 2019, doi: 10.1016/j.optmat.2018.12.054.

[26] Pushparekha, S. Balladka Kunhanna, V. B. Patil, and D. Bikrodi Sesappa, "Studies on characterization of blue emissive chitosan/carbazolyl biphenyl (CRB) composite films and their gamma ray irradiation mediated fluorescence quenching phenomenon," *Optical Materials*, vol. 138, no. February, p. 113675, 2023, doi: 10.1016/j.optmat.2023.113675.

[27] L. Siama and A. Choudhury, "X-aggregates and their Influences on Solid-state Emission of Organoc Luminophores," *Science & Technology Journal*, vol. 8, no. 2, pp. 55–61, 2020, doi: 10.22232/stj.2020.08.02.09.

[28] W. Ji *et al.*, "Tunable Mechanical and Optoelectronic Properties of Organic Cocrystals

by Unexpected Stacking Transformation from H- To J- To X-Aggregation," *ACS Nano*, vol. 14, no. 8, pp. 10704–10715, 2020, doi: 10.1021/acsnano.0c05367.

[29] S. Fatima, A. Mansha, S. Asim, and A. Shahzad, "Absorption spectra of coumarin and its derivatives," *Chemical Papers*, vol. 76, no. 2, pp. 627–638, 2022, doi: 10.1007/s11696-021-01902-6.

Details of Research papers published in journals

1. **B. S. Dayananda**, B. K. Sarojini, Pushparekha, "Stoke's shift and quantum efficiency enhancement in fluorescent coumarin aldehyde (HMCA) dye-conjugated chitosan matrix for optoelectronic applications," *Dyes and Pigments*, 223 (2024), 111936, doi.org/10.1016/j.dyepig.2024.111936. IF 4.5.

2. **B. S. Dayananda**, B. K. Sarojini, Q. A. Wong, C. K. Quah, and P. J. Srijana, "J-aggregation-induced photoluminescence in electrospun pullulan/ 2-(2-fluorophenyl)-3-hydroxy-4H-chromen-4-one composite mat for photonic applications," *Opt. Mater.* vol. 143, 2023, doi: 10.1016/j.optmat.2023.114303. IF 3.9.

3. **B. S. Dayananda**, B. K. Sarojini, Q. A. Wong, C. K. Quah, P. J. Srijana, and Pushparekha, "X-aggregation-induced emission in newly fabricated Pullulan/3-Hydroxyflavone derivative composite electrospun nanofiber mat for optical applications," *Journal of Molecular Structure*, vol. 1286, 135523, 2023, doi: 10.1016/j.molstruc.2023.135523. IF 3.8.

4. **B.S. Dayananda**, B.K. Sarojini, K.R. Harshitha, "Revisiting the pharmacological potential of 3-hydroxy flavone derivatives (3HF) in transdermal drug delivery by electrospun cellulose acetate nanofiber," *ChemistrySelect* (2023), doi.org/10.1002/slct.202202702. 202202702. IF 2.1.

5. B. Balakrishnan, B. K. Sarojini, A. K. Kodoth, **B. S. Dayananda**, R. Ventatesha, "Fabrication and characterization of Tamarind seed gum based novel hydrogel for the targeted delivery of omeprazole magnesium," *Int. J. Biol. Macromol*, 258 (2023), 128758, doi.org/10.1016/j.ijbiomac.2023.128758. IF 8.2.

6. Pushparekha, B. K. Sarojini, V.B. Patil, **B. S. Dayananda**, "Studies on characterization of blue emissive chitosan/carbazolyl biphenyl (CRB) composite films and their gamma-ray irradiation mediated fluorescence quenching phenomenon," *Opt. Mater.* 138 (2023), 113675, https://doi.org/10.1016/j.optmat.2023.113675. IF 3.9.

7. M. Nishitha, B. Narayana, B. K. Sarojini, **B. S. Dayananda**, "Fabrication and characterization of biodegradable hydrogel beads of guar gum for the removal chlorpyrifos pesticide from water," *Int. J. Biol. Macromol*, 277 (2024), 134454, doi.org/10.1016/j.ijbiomac.2024.134454. IF 7.7.

8. K. Shreevani, B. Narayana, B. K. Sarojini, M. Sajida, Suchitra, R. P. Rekha, **B. S. Dayananda**, S. V. Raghu, "Fabrication, characterization and *in vitro* drug release behaviour of electrospun eudragit/eugenol nanofibrous scaffold," *Fibers and Polymers*, 04 (2024), 00622, doi.org/10.1007/s12221-024-00622-4. IF 2.4.

List of Research papers presented in conferences

1. Bikrodi Sesappa Dayananda, Balladka Kunhanna Sarojini, "A study on the frustrated excited-state intramolecular proton transfer phenomenon (ESIPT) in a dual emitter 3-hydroxy flavone derivative," International Webinar on Recent Advances in Chemical Sciences (RACS-2k22), The Gandhigram Rural Institute, Department of Chemistry, Gandhihram-624302, Tamilnadu, India. July 21 & 22, 2022. OP42.

2. Bikrodi Sesappa Dayananda, Balladka Kunhanna Sarojini, "A 3-Hydroxy Flavone Derivative as ESIPT Induced Potential Dual-emitter with Large Stoke's Shift for Display Applications," 11th national conference on condensed matter physics and applications, Manipal Institute of Technology, Manipal, December 14-15th 2023. P35.

List of workshops attended

1. Attended five days National Training Course on "Prerequisites to Recent Advances in Catalysis" Organized by the Department of Chemistry, School of Physical Sciences, Central University of Kerala, Periye, held from 16-20th December 2019.

Signature of the Research Scholar
(B. S. Dayananda)

Signature of the Research Guide
(Prof. B. K. Sarojini)